Predicting positivity for a new era of Alzheimer disease prevention trials

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Alzheimer disease (AD) pathophysiology likely begins years prior to the emergence of clinical symptoms. Biomarker studies suggest deposition of cerebral amyloid may be a necessary and early component of the AD pathophysiologic process.[1] The advent of amyloid imaging techniques with the introduction of Pittsburgh compound B (PiB) in 2004[2] promised the identification of individuals in the presumptive presymptomatic stages of AD.

Autopsy studies have shown that about one-third of older adults have substantial AD neuropathologic changes without cognitive or functional manifestations. Accordingly, amyloid imaging studies demonstrated the presence of cerebral amyloid deposits in 20% to 40% of cognitively normal older adults, although at levels typically less than those observed in individuals with AD. Research criteria[3] were introduced in 2011, defining cognitively normal individuals who test positive for the presence of cerebral amyloid as having "preclinical AD," and plans are underway to target these individuals in large-scale trials assessing therapeutic interventions and their modification of dementia risk.

It is with these future trials in mind that Mielke et al.,[4] in this issue of *Neurology*®, examined common and noninvasive screening measures that might help identify individuals with elevated cerebral amyloid. Their goal was to inform clinical trial design by developing a relatively inexpensive method to enrich a sample of cognitively normal individuals for amyloid positivity and thus reduce the number of individuals who need to be screened. This is an important goal as the coming wave of prevention trials will need to screen out up to 80% of potential participants who are amyloid negative, at a considerable expense and burden that could limit the size and power of such studies. To put this in perspective, in a trial such as the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) using amyloid-PET to screen 3,200 amyloid-negative subjects so as to arrive at ~800 amyloid-positive subjects (400 each in placebo and treatment arms), screening would add approximately $8,000,000 to the cost of the trial.

Mielke et al. examined a large number (n = 483) of cognitively normal older adults (ages 70–92 years) from a population-based cohort characterized by PiB-PET. Participants were classified as being amyloid-positive using 2 different cutpoints, with 44% of the group classified as amyloid-positive using the more lenient cutpoint (cortical to cerebellar PiB uptake >1.4) and 31% amyloid-positive using a higher cutpoint (>1.5). The investigators tested the predictive value of age, sex, *APOE* genotype, family history, cognitive performance, and subjective cognitive complaints.

Not surprisingly, given findings from prior studies,[5] the best indicators of the presence of cerebral amyloid were age and *APOE* ε4. For every 5-year increase in age, the odds of being amyloid-positive increased 40%–45%, while *APOE* ε4 carriers were 3 times more likely to be amyloid-positive. Other significant predictors of cerebral amyloid positivity included family history of AD, reduced cognitive performance on an extensive neuropsychological battery, and subjective memory complaints. Interestingly, subjective memory complaints were as good at predicting amyloid presence as the extensive battery of cognitive tests, suggesting that assessing memory complaints is as effective as cognitive performance for predicting amyloid positivity. Additionally, the data suggest that the predictive value of the variables (with the exception of cognitive performance) appears to be attenuated in the older age group (>80 years), further underscoring the importance of age in screening for amyloid positivity.

The main limitation to the practical value of these findings is that using the best-performing predictors to enrich clinical trial samples—advanced age and *APOE* ε4 carrier status—would severely limit the generalizability of the findings. For instance, limiting trials to subjects over age 80 or to ε4-positive subjects would miss a sizable target population and, as

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the authors note, restrict the labeling uses of any new therapy granted by a regulatory agency. An additional limitation is the exclusion of participants under the age of 70 years; it is in this age range that screening methods may have the biggest effect on enriching trial populations, given the lower prevalence of amyloidosis.

US Food and Drug Administration approval of the ^{18}F-based amyloid imaging agent florbetapir this year will ensure widespread availability of amyloid imaging and could further stimulate a wave of AD prevention trials. Nonetheless, it is important to note that the clinical importance of asymptomatic amyloid plaques remains imprecisely defined. Although the concept of preclinical AD posits that cerebral amyloid deposition in cognitively normal adults represents a presymptomatic stage of AD, autopsy studies clearly demonstrate that not all amyloid-positive individuals will develop a dementia syndrome prior to their death. Additionally, the magnitude and timing of risk associated with asymptomatic cerebral amyloidosis is not yet well-defined. Without clear knowledge of these risks, and in the absence of effective interventions to delay the onset of dementia, the use of amyloid imaging in unaffected, cognitively normal participants should be restricted to the research arena, such as is planned for the prevention trials. Additionally, since it is unlikely that amyloid-negative subjects will be included in prevention trials, participation in these trials will reveal the participant's positive amyloid status. This requires careful consideration of how participants will be informed and counseled about this information.

Although there remain a number of important unknowns, early studies suggest the presence of cerebral amyloid is not benign and thus support the use of amyloid imaging for identifying an important target cohort for AD prevention trials. For instance, results from early studies suggest that asymptomatic cerebral amyloid is associated with cognitive decline,[6] brain atrophy,[7] and altered brain function,[8,9] supporting the concept of targeting this population for testing dementia-delaying strategies. The findings from the Mielke et al. study suggest that inexpensive and noninvasive measures can be used to reduce the number of cognitively normal individuals who need to be screened for these trials; the data thereby represent useful information for ushering in a new era of AD prevention studies.

DISCLOSURE

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